Radical-mediated Anti-Markovnikov Hydrophosphonation of Olefins

Christopher S. Daeffler and Robert H. Grubbs

Division of Chemistry and Chemical Engineering
California Institute of Technology MC 164-30
Pasadena, California 91125

rhg@caltech.edu

Table of Contents

General Information

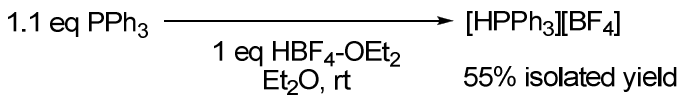
NMR spectra were recorded in $CDCl_3$ on Varian Mercury 300 MHz or INOVA 500 MHz spectrometers in the High-Resolution Nuclear Magnetic Resonance Facility at the California Institute of Technology (Caltech), unless otherwise noted. ^{1}H and ^{13}C chemical shifts are referenced relative to $CDCl_3$ (δ=7.27 for ^{1}H and δ=77.23 for ^{13}C). ^{19}F and ^{31}P chemical shift are referenced automatically by the VnmrJ software program. Spectral analysis was performed on MestReNova software. High-resolution mass spectra were provided by the Caltech's Mass Spectrometry Facility.

Photoreactions were performed using a 450 W medium pressure mercury arc lamp (Ace Glass) equipped with a water-cooled quartz jacket. The reaction vessels were Pyrex tubes sealed with PTFE closures. Pyrex glass has 90% transmittance at 350 nm.

Materials

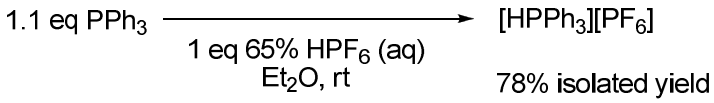
CH_2Cl_2 and THF were purified by passage through solvent purification columns by the method of Grubbs *et al.*[1] PhCl was purified by distillation from P_2O_5 under nitrogen atmosphere. Triphenylphosphine (PPh_3) was purified recrystallization from EtOH. 1-hexene was vacuum-transferred from CaH_2 before use. 1,1'-azobisisobutyronitrile (AIBN) was purified by recrystallization from Et_2O. 1,1′-azobis(cyclohexanenitrile) (ACN) was purified by recrystallization from MeOH. All other commercially available materials were obtained from Aldrich Chemical Company and used as received unless otherwise noted.

Triphenylphosphonium tetrafluoroborate, $[HPPh_3][BF_4]$



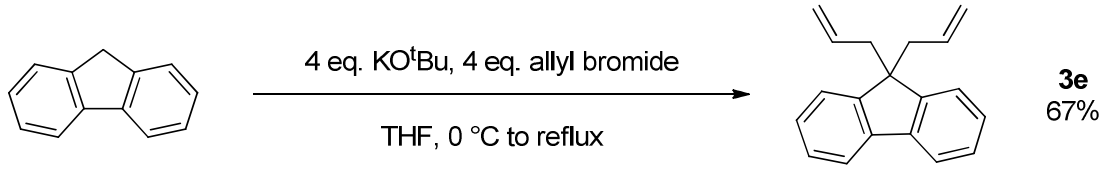
To a 300 ml Erlenmeyer flask equipped with a stirbar was added PPh_3 (29.5 g, 112 mmol, 1.1 eq). The PPh_3 was dissolved in Et_2O (150 ml). Upon addition of HBF_4 in Et_2O (54 wt%, 14 ml, 100 mmol, 1 eq), a white solid precipitated. The white solid was collected by filtration and washed with Et_2O. Recrystallization of the solid from $CHCl_3$ (60 ml) gives $[HPPh_3][BF_4]$ as colorless prisms in 55% yield (21.4 g, 55 mmol). A discussion of synthesis, characterization and acidity of $[HPR_3][BF_4]$ salts is presented in references 2 and [3]

Triphenylphosphonium hexafluorophosphate, $[HPPh_3][BF_4]$



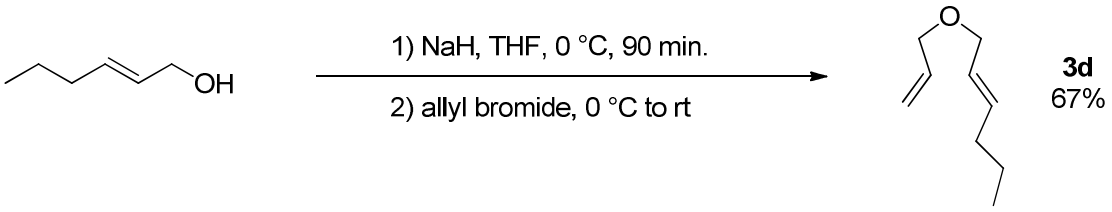
A 50 ml roundbottom flask was equipped with a stirbar and dried under vacuum. Under Ar flow, the flask was charged with PPh_3 (2 g, 7.6 mmol, 1.1 eq.), which was dissolved in Et_2O (10 ml). A 65% aqueous solution of HPF_6 (0.9 ml, 6.6 mmol, 1 eq) was added to the ethereal solution and a white solid precipitated. The white solid, $[HPPh_3][PF_6]$, was collected by filtration in 78% yield (2 g, 5.1 mmol) and used without further purification.

9,9-diallylfluorene (3b).



A flame-dried 250 ml Schlenk flask with a stirbar was charged with KO^{t}Bu (1.2 g, 20 mmol, 2 eq.), then evacuated and backfilled with Ar. The flask was cooled to 0 °C in an ice water bath. THF (100 ml) was transferred to the cooled flask *via* cannula. Fluorene (1.7 g, 10 mmol, 1 eq.) was added in one portion. The solution was stirred at 0 °C for 20 minutes, during which time the solution changed from colorless to orange. Allyl bromide (850 µl, 20 mmol, 2 eq) was added dropwise and the solution turned from orange to bright green. The solution was allowed to warm overnight to room temperature. Additional KO^{t}Bu (2 eq.) and allyl bromide (2 eq.) was added to the reaction and it was refluxed for 4 hours. When the reaction was complete, it was cooled to room temperature and quenched with MeOH, the water. The remaining water was removed by $MgSO_4$, and all solids were filtered off. Excess solvent was removed by rotary evaporation to yield viscous oil. The oil was further purified by silica gel chromatography (hexanes, R_f=0.22) to yield 9,9-diallylfluorene (1.7 g, 6.7 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (2H, d, *J* = 8 Hz), 7.44 (2H, d, *J* = 7 Hz), 7.36-7.31 (4H, m), 5.33-5.24 (2H, m), 4.86 (2H, dd, *J* = 17 Hz, 1 Hz), 4.77 (2H, d, *J* = 10 Hz), 2.74 (4H, d, *J* = 7 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.29, 140.71, 133.73, 127.08, 126.91, 123.62, 119.76, 117.48, 54.16, 43.49. HRMS (EI+): calculated = 246.1408, found = 246.1408.

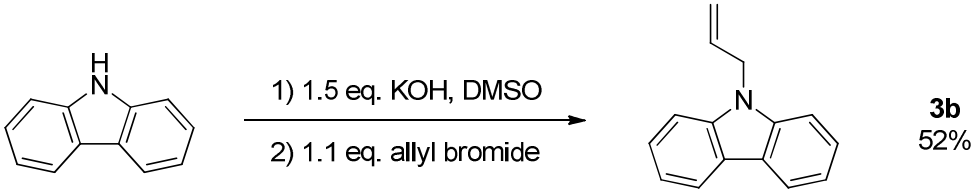
Allyl *trans*-2-hexenyl ether (3d).



A 2-neck 250 ml roundbottom flask was fitted with a PTFE valve inlet and a septum. The flask was flame-dried. THF (100 ml) was transferred to the flask *via* cannula. The flask was then

cooled to 0 °C in an ice bath and NaH (60% in mineral oil, 1.1 g, 27.5 mmol, 1.1 eq) was added. Dropwise, *trans*-2-hexen-1-ol (2.9 ml, 25 mmol, 1 eq) was added to the suspension. The reaction was allowed to stir for 90 minutes at 0 °C. Allyl bromide (2.3 ml, 27.5 mmol, 1.1 eq) was added dropwise to the cooled reaction. The mixture was allowed to warm overnight to room temperature. The reaction was quenched with water (50 ml). The aqueous layer was extracted with hexanes (2x25 ml), then the combined organic layers were washed with brine (50 ml). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. The crude oil was purified by silica gel chromatography (9:1 hexanes:ethyl acetate) to yield allyl *trans*-2-hexenyl ether (2.3 g, 16 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (1H, m)), 5.70 (1H, m), 5.59 (1H, m), 5.29 (1H, d, *J* = 17.2), 5.19 (1H, d, *J* = 9.9), 3.98 (2H, dd, *J* = 5.7, 1.2), 3.95 (2H, d, *J* = 6.2) 2.04 (2H, dd, *J* = 14.5, 6.9), 1.43 (dq, *J* = 14.8, 7.4, 2H), 0.92 (t, *J* = 7.4, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.81, 126.23, 116.98, 70.92, 34.38, 29.69, 22.22, 21.14, 13.69. HRMS (EI+): calculated = 140.1201, found = 140.1215.

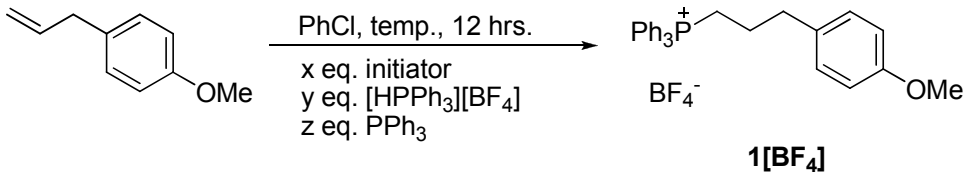
Allyl carbazole (3b).



Carbazole (3.3 g, 20 mmol, 1 equiv.), KOH (1.6g, 30 mmol, 1.5 equiv.) and NaI (160 mg, 1 mmol, 0.1 eq) were dissolved in DMSO (20 ml) in a 100 ml roundbottom flask. Once all solids were dissolved, allyl bromide (1.8 ml, 22 mmol, 1.1 equiv.) was added *via* syringe. The flask was capped and stirred at room temperature over night. Water (25 ml) was added to the reaction and large amount of yellow solid crashed out. The solid was filtered and recrystallized from

hexanes to give yellowish-brown crystals (2.2 g, 10.4 mmol, 52% isolated yield). Characterization matches the previously published data.[4]

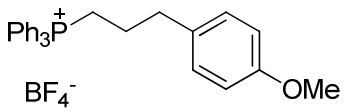
General Setup for Conditions Screen with Standard Radical Initiators



1[BF_4]

A Schlenk tube with a stirbar and PTFE closure was flame-dried under vacuum. The tube was backfilled under Ar atmosphere. The appropriate amounts of initiator, [$HPPh_3$][X] and PPh_3 were added to the tube. The tube was then charged with the correct solvent (5 ml) and 4-allylanisole (24 µl, 0.15 mmol). The tube was sealed and heated to the appropriate temperature in an oil bath (AIBN: 80 °C; ACN: 110 °C; DBP: 110 °C). After 12 hours, the tube was removed from the oil bath and cooled. The solvent was removed by rotary evaporation and the conversion was measured by ^{1}H NMR. If the reaction required a pulsed addition of initiator and/or [$HPPh_3$][BF_4], the tube was removed from the oil bath after 6 hours, the additional reagents were added under Ar flow, the tube was resealed and heated for the final 6 hours. The products were analyzed by ^{1}H NMR.

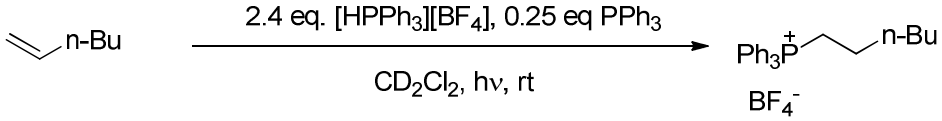
1[BF_4].



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.76 (3H, m), 7.72 – 7.56 (12H, m)), 7.10 (2H, d, *J* = 8.7), 6.82 (2H, d, *J* = 8.7), 3.79 (3H, s), 3.35 – 3.20 (2H, m), 2.86 (2H, t, *J* = 7.1), 1.89 (2H, d, *J* =

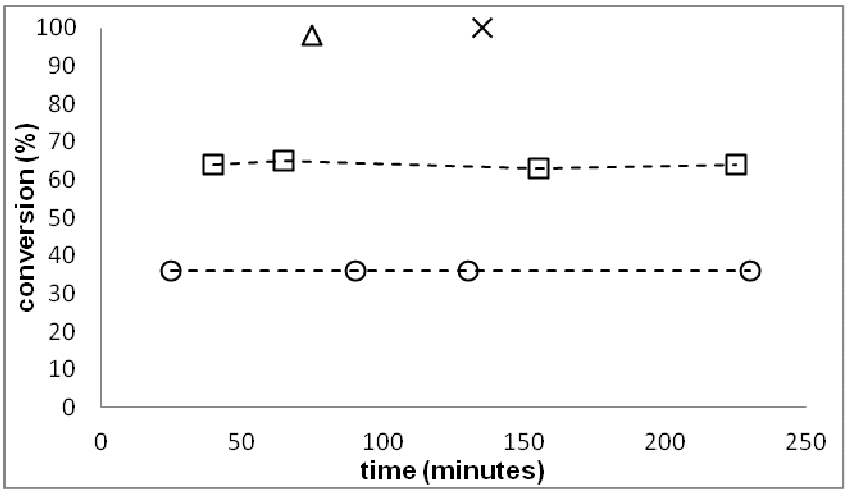
8.2). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 158.21, 135.10 (d, J_{P-C} = 3.0), 133.38 (d, J_{P-C} = 9.9), 131.92, 129.90, 130.50 (d, J_{P-C} = 12.5), 118.05 (d, J_{P-C} = 86.1), 114.04, 55.28, 34.64 (d, J_{P-C} = 16.8), 24.71 (d, J = 4), 20.69 (d, J_{P-C} = 51.7).

NMR-scale Kinetic Analysis of Photochemical Hydrophosphonation.

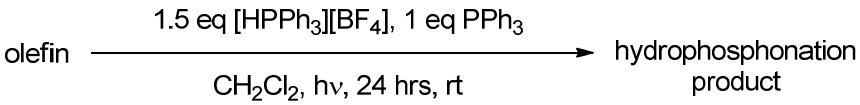


2[BF$_4$]

In a nitrogen-filled glovebox, 1-hexene (38 μl, 0.3 mmol, 1 eq), $[HPPh_3][BF_4]$ (268 mg, 0.75 mmol, 2.4 eq), PPh_3 (20 mg, 0.075 mmol, 0.25 eq) and 1,3,5-trimethoxybenzene (6.7 mg, 0.04 mmol, internal standard) were dissolved in CD_2Cl_2 (5 ml). The solution was divided into aliquots (5x1 ml) and placed in five screw-cap NMR tubes. The sealed tubes were removed from the glovebox. The NMR tubes were irradiated simultaneously in a photobox, and removed at the indicated intervals (O, 25 minutes; □, 40 minutes; Δ, 75 minutes; X, 135 minutes). Conversion was calculated from comparison to the 1,3,5-trimethoxybenzene internal standard. The spectral properties of **2[BF$_4$]** were similar to that of is commercially available bromide analogue.



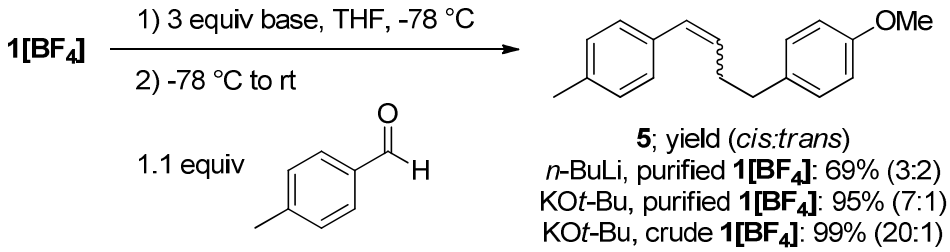
General Photochemical Hydrophosphonation Conditions.



A Pyrex Schlenk tube equipped with a stirbar and PTFE closure was flame-dried under vacuum. The tube was backfilled with Ar and charged with $[HPPh_3][BF_4]$ (525 mg, 1.5 mmol, 1.5 eq) and PPh_3 (262 mg, 1 mmol, 1 eq). The tube was evacuated and backfilled with Ar. The solids were dissolved in CH_2Cl_2 (10 ml). The substrate (1 mmol) was added in one portion. The Schlenk tube was sealed and placed in the photobox for 24 hours. The solvent was removed from the reaction mixture *via* rotary evaporation. The hydrophosphonation products were purified as outlined below.

Compound	Purification	Appearance
1[BF_4]	trituration with EtOac	powder
4a	*in vacuo*	amorphous
4b	trituration with EtOac	powder
4c	silica gel chromatography with acetone	amorphous
4d	silica gel chromatography with acetonitrile	amorphous
4e	trituration with EtOac then hexanes	powder

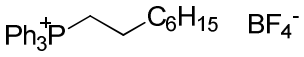
Wittig Olefination with 1[BF_4] for the synthesis of styrene 5.



A 50-ml Schlenk flask equipped with a stirbar was flame-dried under vacuum. The flask was backfilled with Ar. Under Ar flow, the flask was charged with **1[BF_4]** (500 mg, 1 mmol, 1 eq.), then evacuated and backfilled. The flask was cooled to -78 °C in a CO_2(s)/acetone bath and charged with THF (12 ml). Potassium *t*-butoxide (340 mg, 3 mmol, 3 eq.) was added to the cooled suspension in one portion. The reaction mixture was allowed to stir for 30 minutes at -78 °C, becoming dark red. *Via* syringe, *p*-tolualdehyde (240 µl, 2 mmol, 2 eq.) was added to the solution. The reaction mixture was allowed to very slowly warm overnight. The reaction was quenched first with methanol (2 ml), then water (2 ml). The layers were separated. The aqueous layer was extracted with diethyl ether (2x20 ml). The combined organic layers were washed with brine (20 ml), dried over $MgSO_4$ and filtered. Excess solvent was removed by rotary

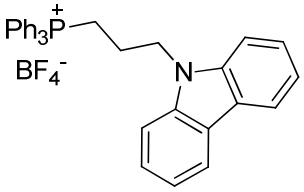
evaporation. Characterization for *Z*-**5** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 – 7.12 (m, 6H), 6.85 (m, 2H), 6.42 (d, *J* = 11.7, 1H), 5.66 (dt, *J* = 11.6, 7.0, 1H), 3.81 (s, 3H), 2.73 (m, 2H), 2.64 (dd, *J* = 15.0, 7.9, 2H), 2.35 (2, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.82, 136.23, 134.71, 133.65, 131.21, 129.16, 128.69, 128.51, 128.45, 113.75, 55.26, 35.20, 30.71, 21.16. HRMS (EI+): calculated = 252.1514, found = 252.1515.

Octyltriphenylphosphonium Tetrafluoroborate (4a).



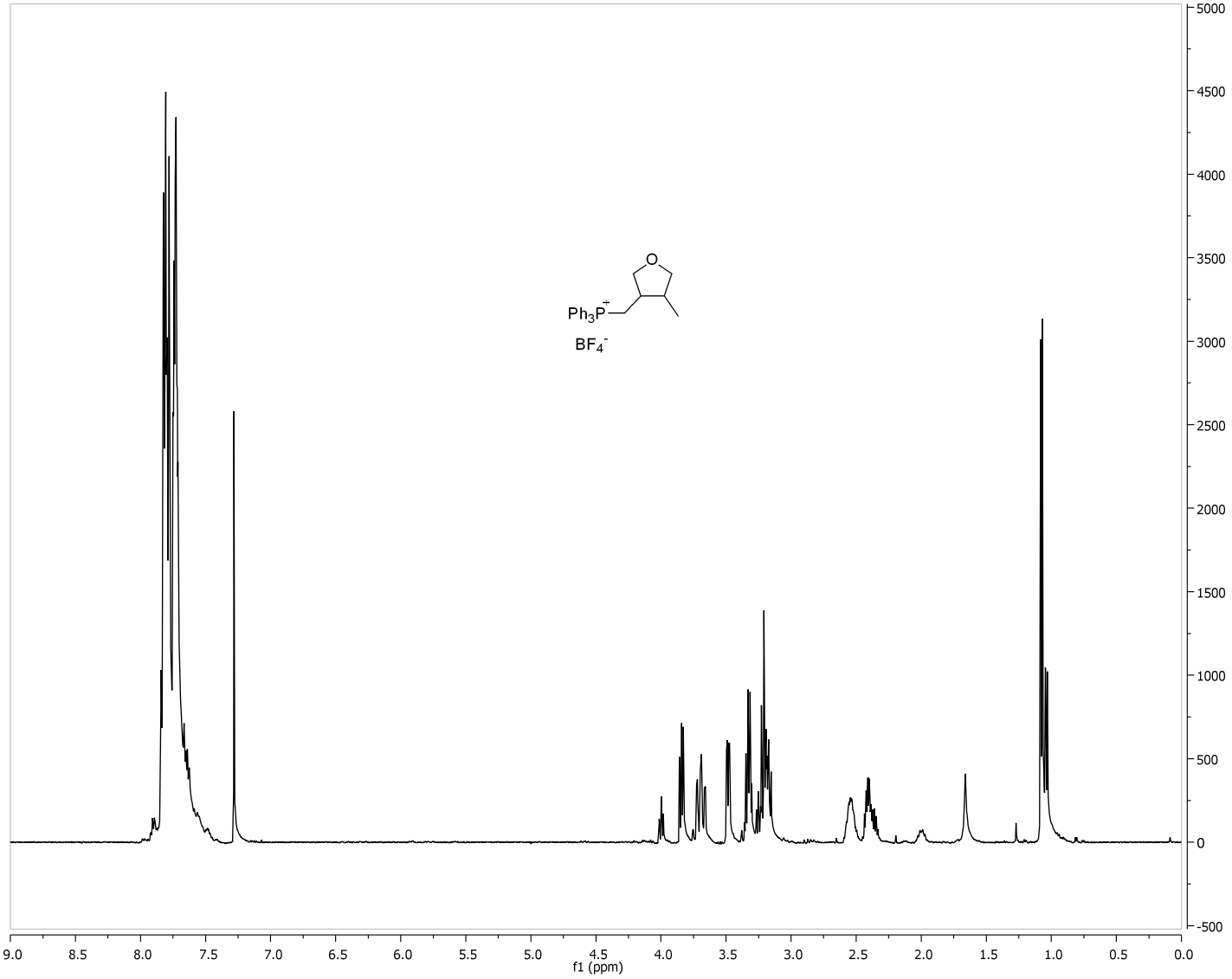
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (m, 3H), 7.72 (m, 12H), 3.24 (m, 2H), 1.58 (b, 4H), 1.20 (b, 8H), 0.84 (t, *J* = 7.0, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.16 (d, $J_{P\text{-}C}$ = 3.0), 133.39 (d, $J_{P\text{-}C}$ = 9.9), 130.56 (d, $J_{P\text{-}C}$ = 12.5), 118.13 (d, $J_{P\text{-}C}$ = 86.0), 44.99, 31.63, 30.31 (d, $J_{P\text{-}C}$ = 15.8), 28.96 (d, $J_{P\text{-}C}$ = 1), 28.83, 22.54, 21.95 (d, $J_{P\text{-}C}$ = 51.0), 14.04. HRMS (FAB+): calculated = 375.2242, found = 375.2250.

Hydrophosphonation product 4b.

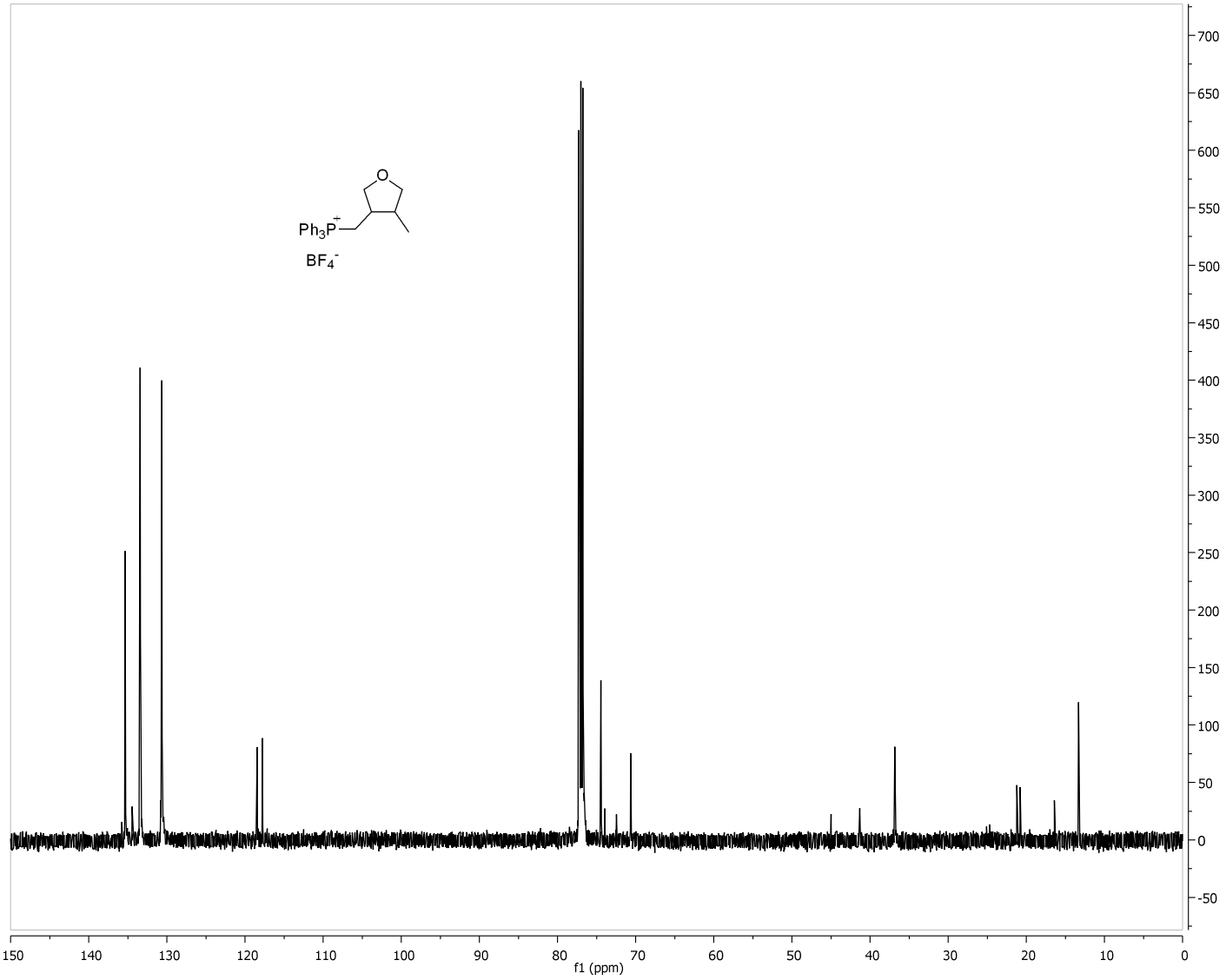


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.7, 2H), 7.74 (m, 2H), 7.67 (m, 2H), 7.59 (m, 2H), 7.54 – 7.40 (m, 12H), 7.24 (t, *J* = 6.9, 3H), 4.66 (t, 2H, *J* = 6), 3.35 (m, 2H), 2.326 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.28, 134.97, 133.21 (d, $J_{P\text{-}C}$ = 9.9), 130.36 (d, $J_{P\text{-}C}$ = 12.6), 129.24 (d, $J_{P\text{-}C}$ = 13.5), 126.25, 122.79, 120.19, 119.23, 117.65 (d, $J_{P\text{-}C}$ = 86.4), 109.14, 42.03 (d, $J_{P\text{-}C}$ = 19.1). HRMS (FAB+): calculated = 470.2038, found = 470.2054.

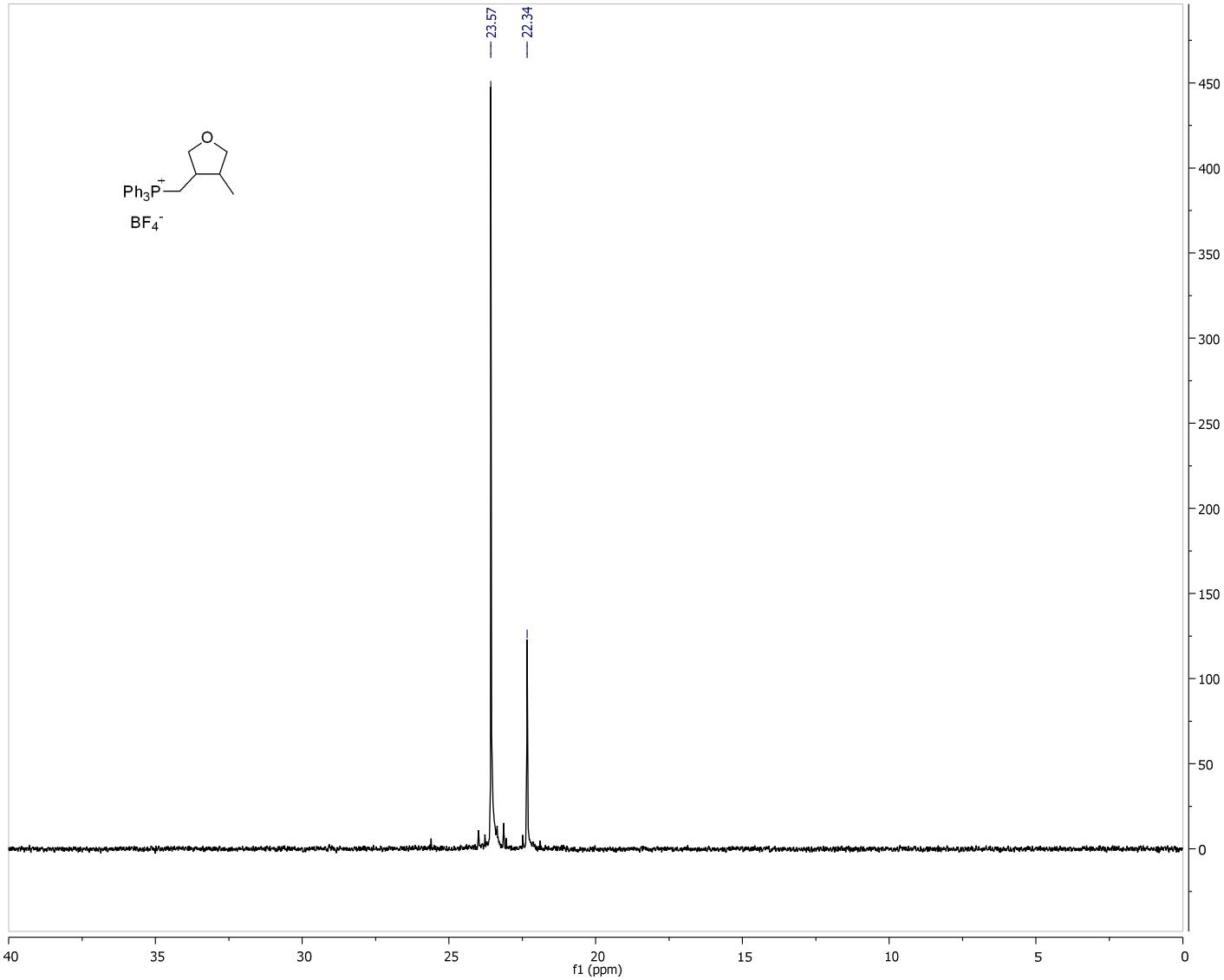
Compound 4c, ^{1}H NMR (500 MHz, $CDCl_3$



Compound 4c, $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$)

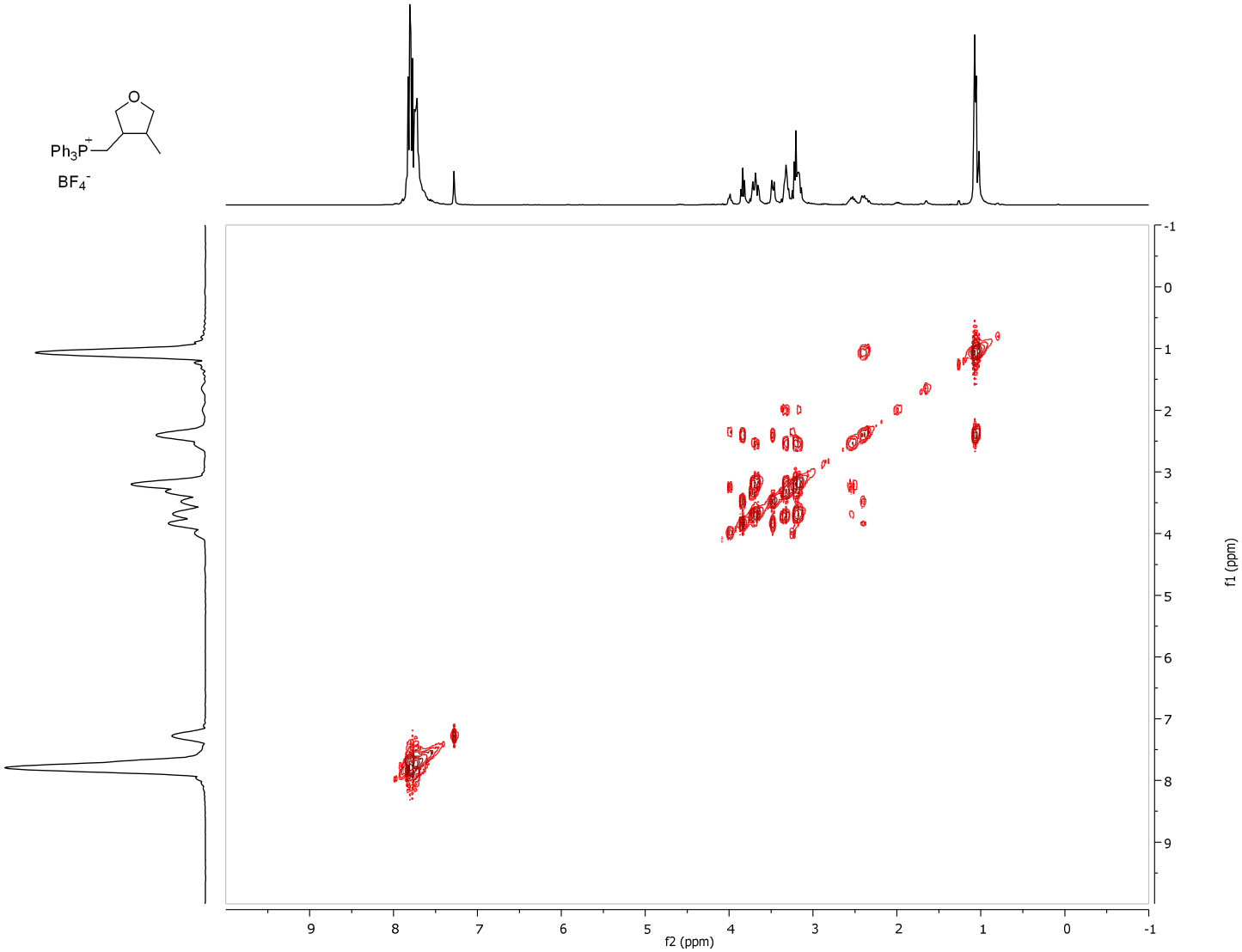


Compound 4c, $^{31}P\{^{1}H\}$ (202 MHz, $CDCl_3$)

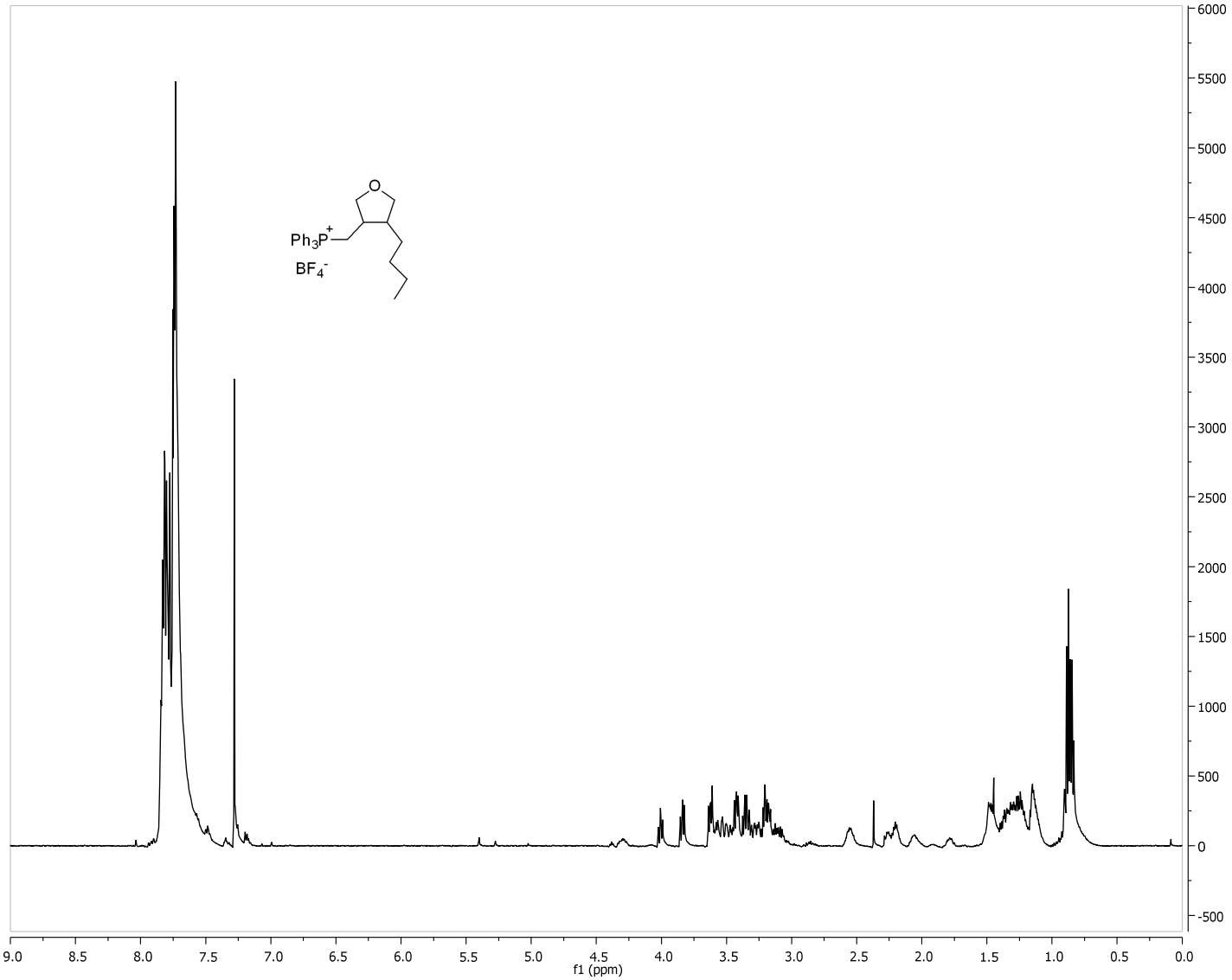


Compound 4c, ^{31}P HMBC (202 MHz, $CDCl_3$)

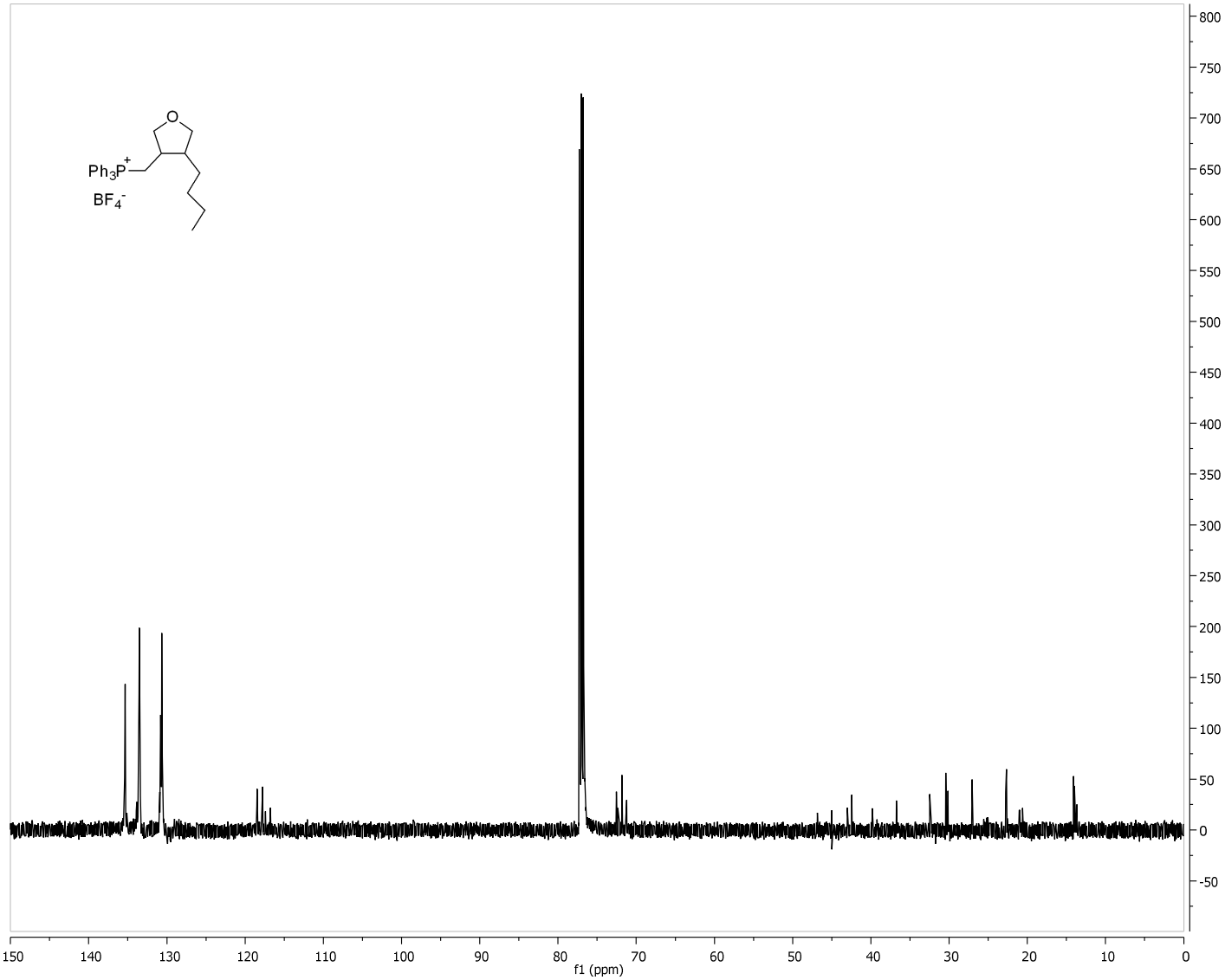
Compound 4c, ^{1}H COSY (500 MHz, $CDCl_3$)



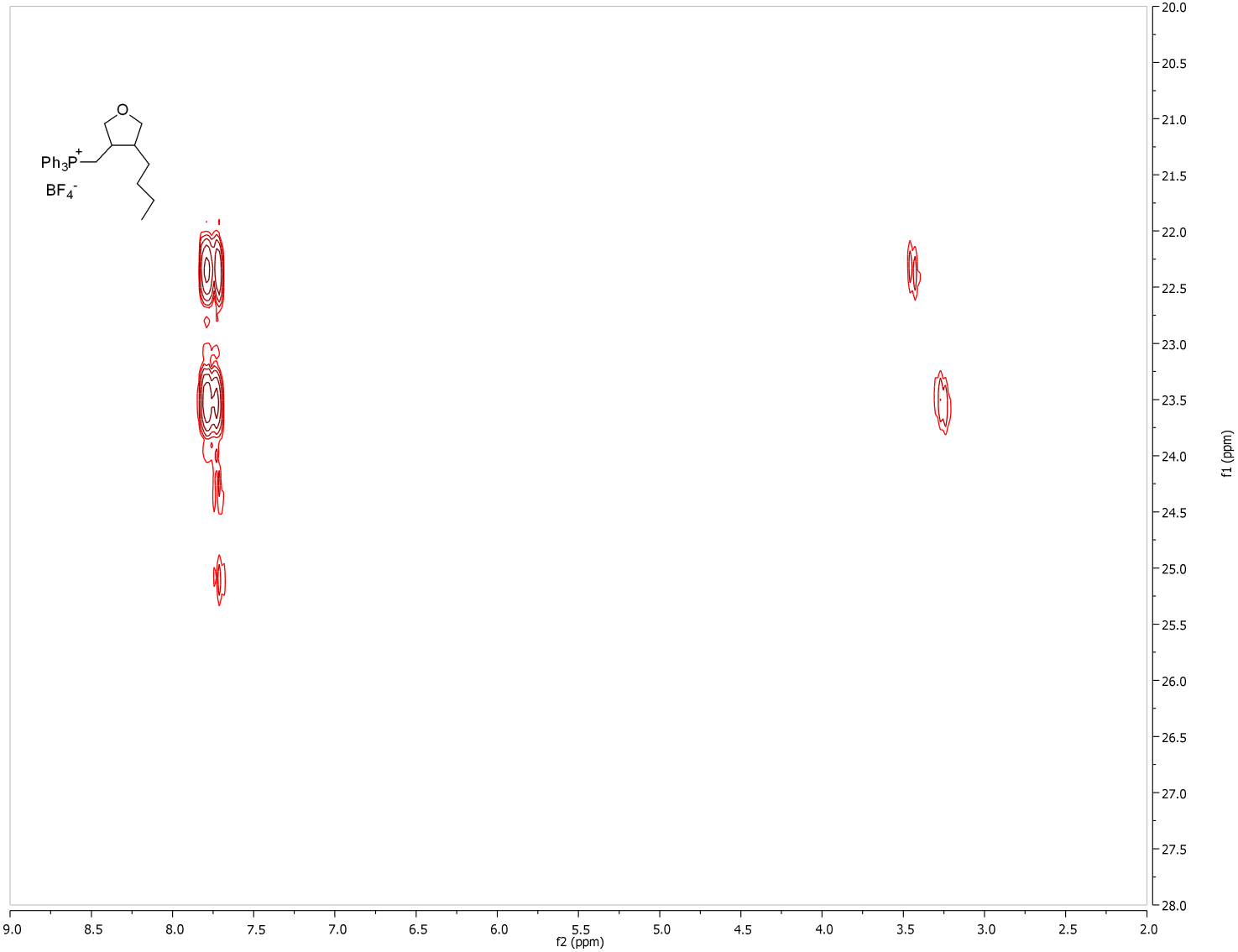
Compound 4d, ^{1}H NMR (500 MHz, $CDCl_3$



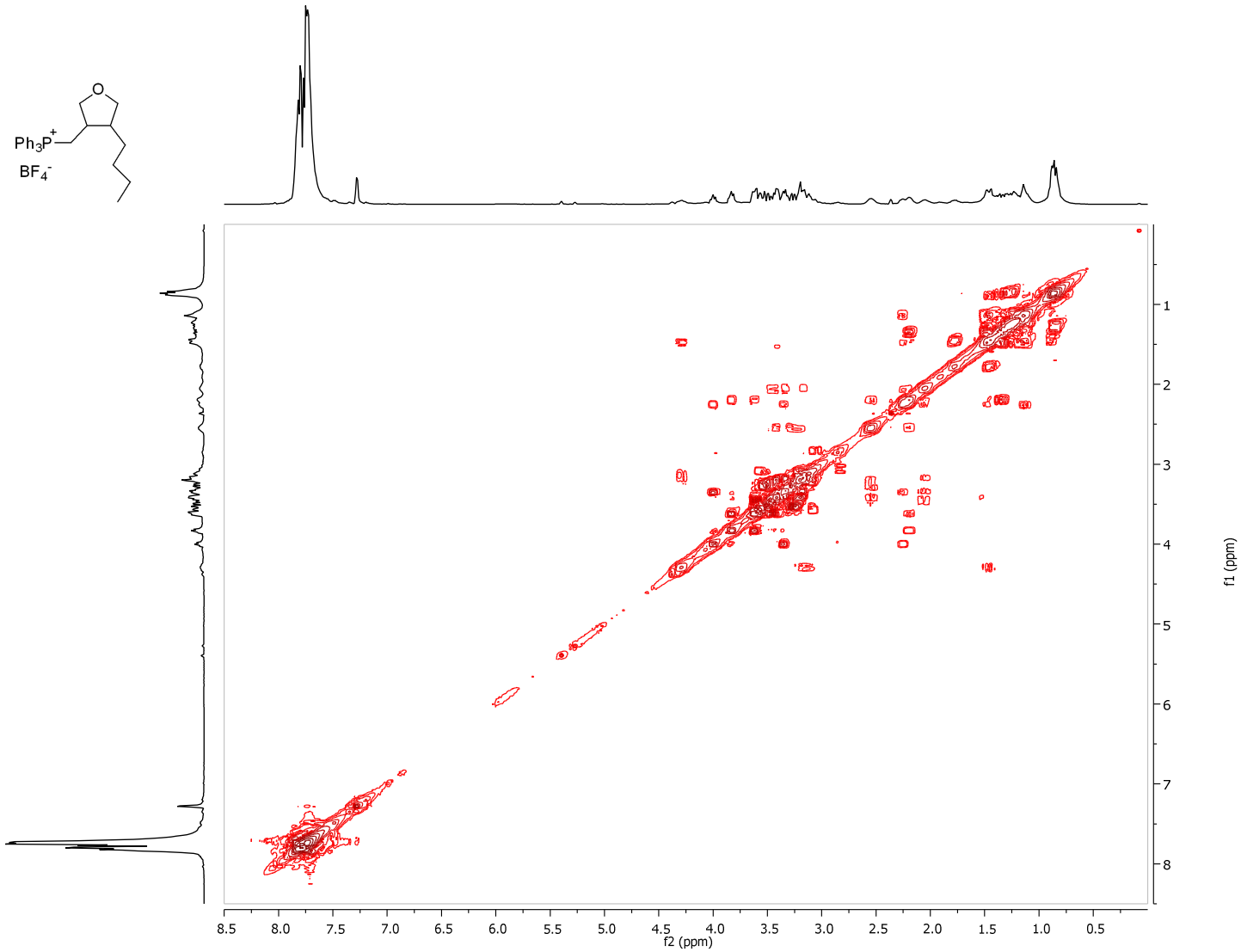
Compound 4d, $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$)



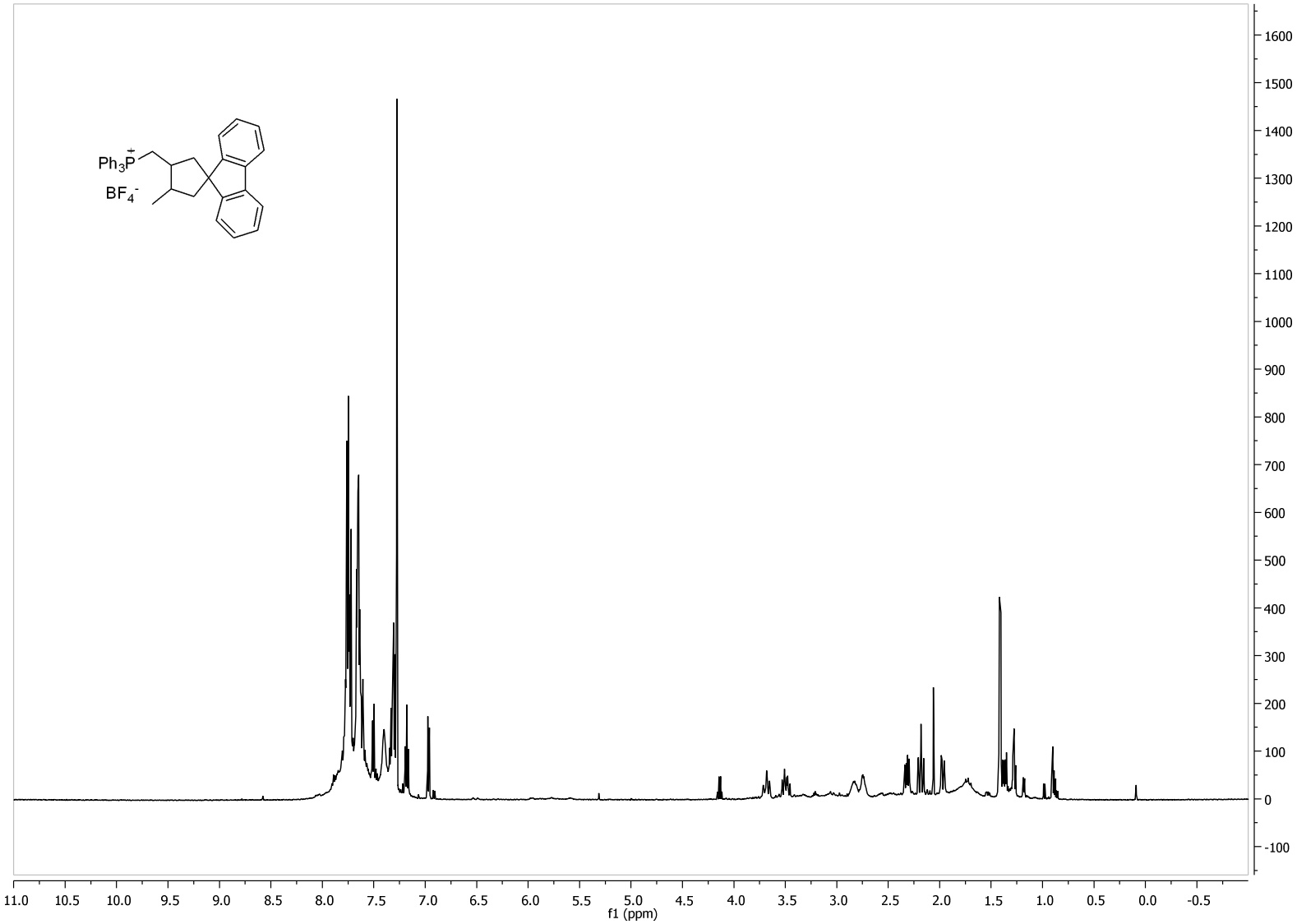
Compound 4d, ^{31}P HMBC (202 MHz, $CDCl_3$)



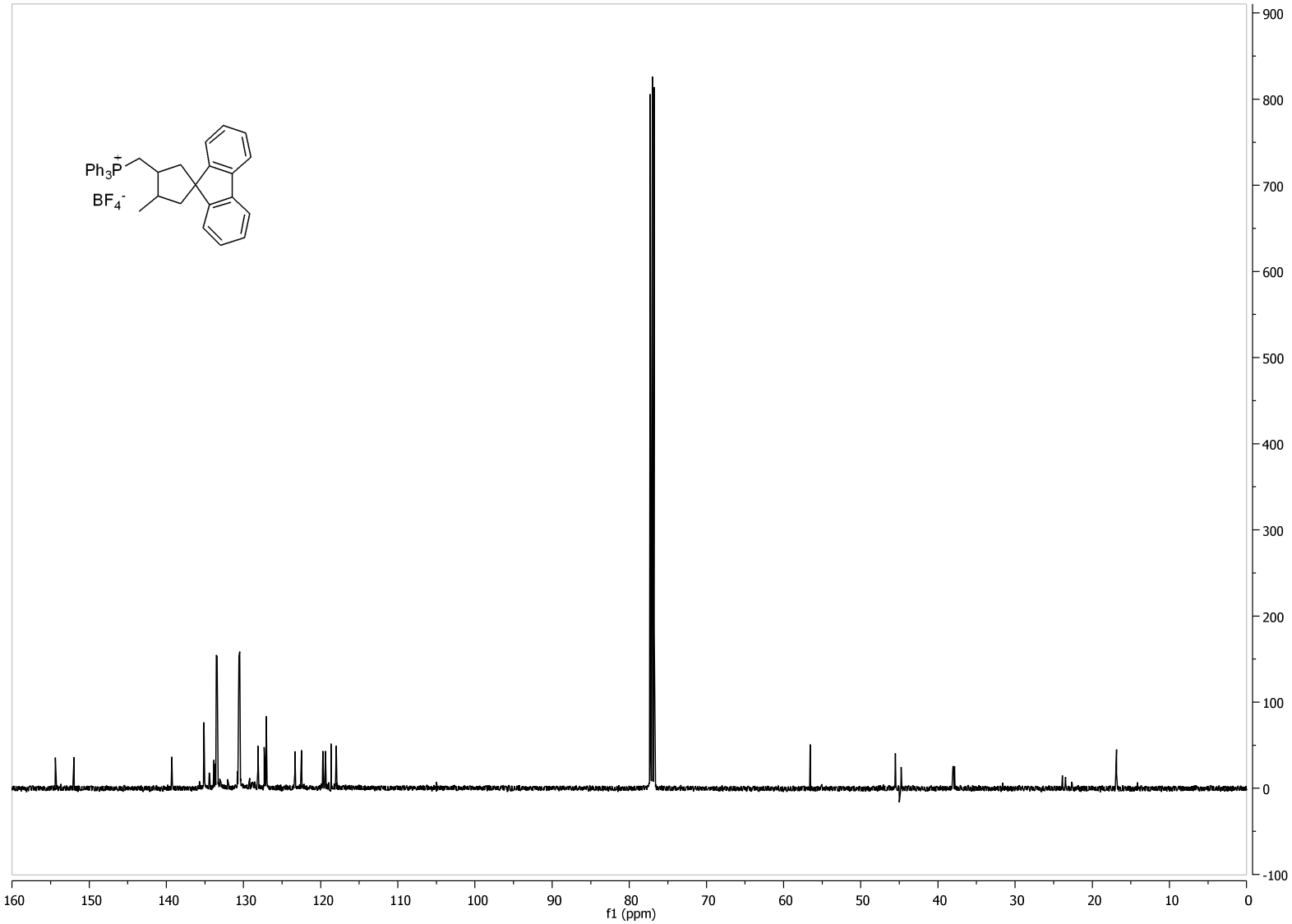
Compound 4d, ^{1}H COSY (500 MHz, $CDCl_3$)



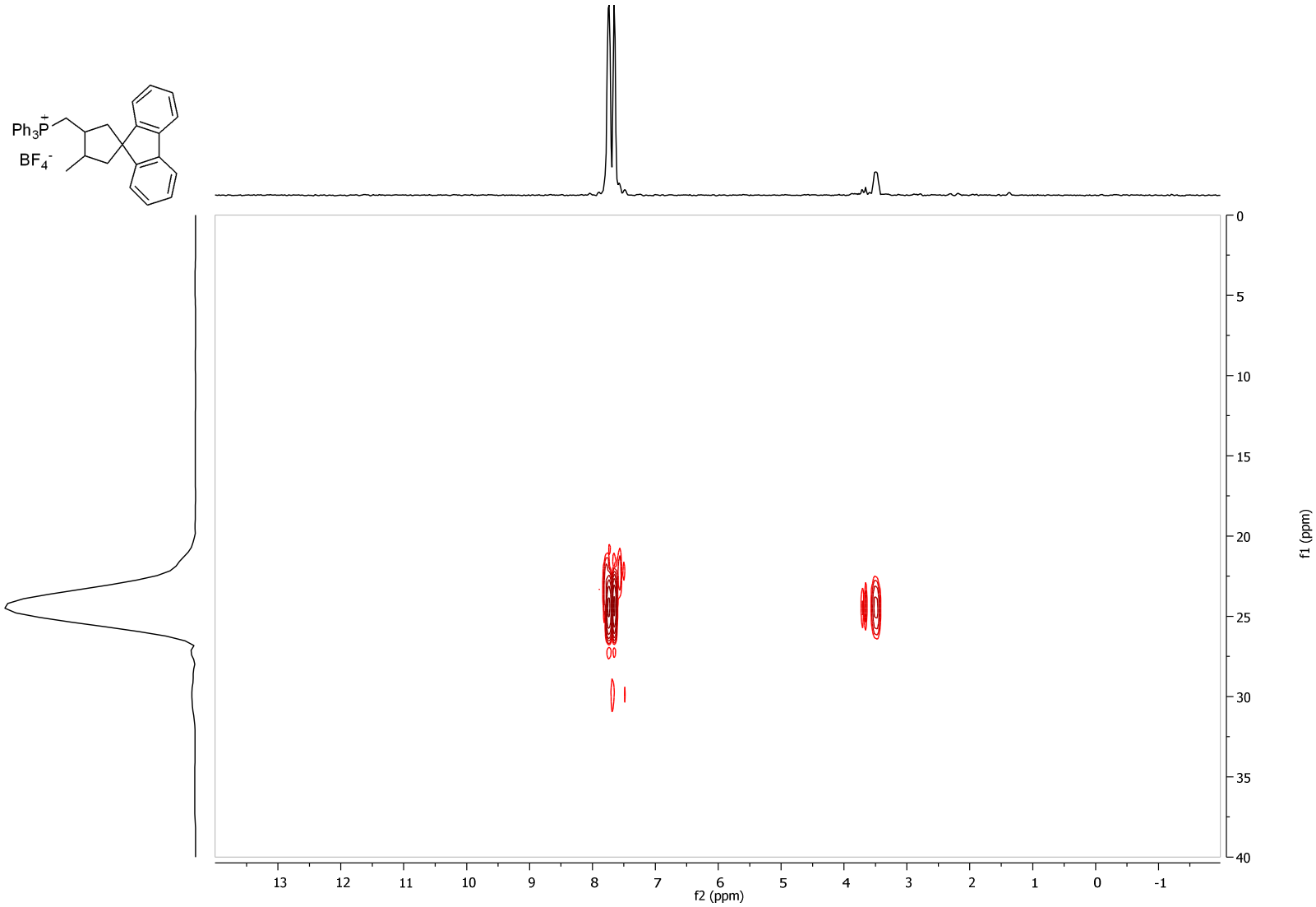
Compound 4e, ^{1}H NMR (500 MHz, $CDCl_3$



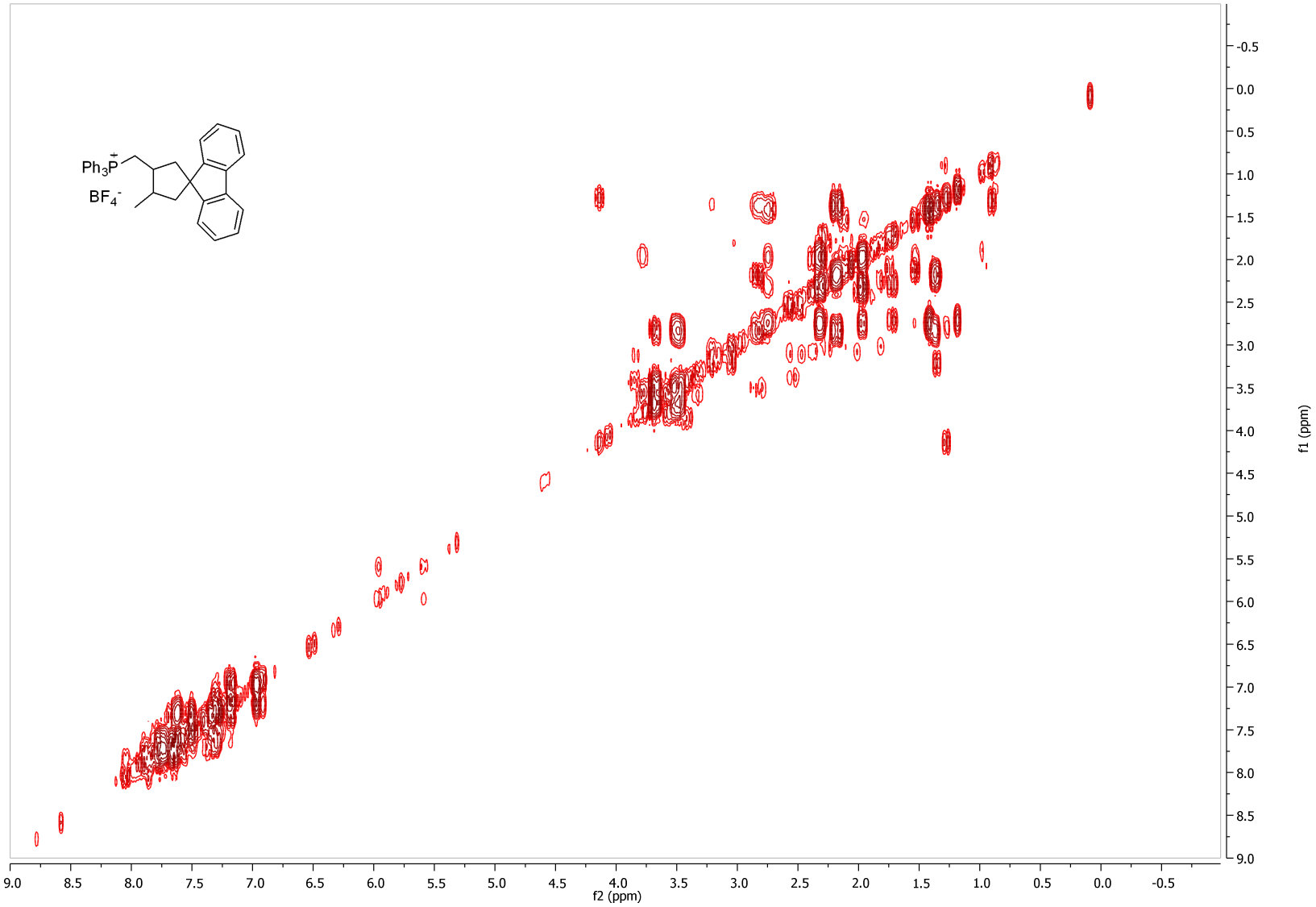
Compound 4e, $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$)

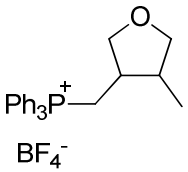


Compound 4e, ^{31}P HMBC (202 MHz, $CDCl_3$)

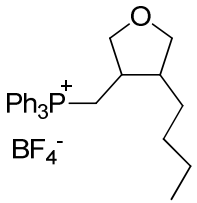


Compound 4e, ^{1}H COSY (500 MHz, $CDCl_3$)

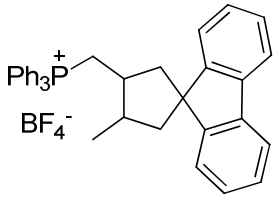




4c
calculated=361.1721
found=361.1706



4d
calculated=403.2191
found=403.2200



4e
calculated=509.2398
found=509.2394

[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
[2] Li, T.; Lough, A. J.; Zuccaccia, C.; Macchioni, A.; Morris, R. H. *Can. J. Chem.* **2006**, *84*, 164-175.
[3] Li, T.; Lough, A. J.; Morris, R. H. *Chem. Eur. J.* **2007**, *13*, 3796-3803.
[4] Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184.